David Fass, submitted in the enclosed Declaration under 37 C.F.R. §1.132, and enclosed copies of a number of publications showing the acceptability of the pig as an animal model for blood clotting. Also enclosed is a copy of the decision of In re Argoudelis 434 F.2d 1390 (C.C.P.A. 1970), as discussed below.

Rejections under 35 U.S.C. § 112, First Paragraph

The specification has been objected to and Claims 1-9 and 11-16 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention. These objections and rejections are respectfully traversed.

The requirement under 35 U.S.C. §112 is that applicant must provide a written description of how to make and use the claimed invention, i.e., a method of inhibiting microvascular bleeding such as exists at the surface of a burn wound, and a composition for administration to a patient of an inhibitor of a natural anticoagulant in combination with a topical coagulant.

Pages 6-14 provide a clear description of those inhibitors defined by the independent claims and inhibitors thereof; page 13 describes the topical coagulants that are available. Pharmaceutically acceptable carriers are described at page 14, lines17-20.

The effective dosage of inhibitor of an anticoagulant is described at page 14, lines 21-27, and page 15, line 29 to page 16, line 24. The effective dosage of the topical coagulant is described at page 16, lines 25-31.

Topical coagulants and effective dosages are also well known to those skilled in the art; see, for example, Furie, et al., Cell 53, 505-518 (1988); Suzuki, et al., Thrombosis Res. 53, 271-277 (1989); and U.S. Patent No. 5,130,244, copies of which were submitted with the last reponse.

The example at pages 17 to 21 demonstrates reduction to practice and efficacy of the claimed composition.

Pages 13 to 14 describe the disorders which can be treated. The example at pages 17 to 21 demonstrates actual reduction to practice using pigs as an animal model.

As discussed in the Office Action and during the telephone interview, the basis for the rejection appears to be the Examiner's belief that the method would require undue experimentation and that pigs are not predictive of efficacy in humans.

Pigs are predictive of human blood coagulation

The claimed method and composition are in the field of coagulation. Dr. Fass is an expert in the field of coagulation. As demonstrated by Dr. Fass' Declaration and accompanying publications, pigs are an acceptable animal model for coagulation in humans in general, and microvascular bleeding in particular. Moreover, coagulation is not an "unpredictable art" *per se*, although as discussed below the claimed method and compositions were not obvious. These comments are equally applicable to the speculation at the bottom of page 4 of the office action regarding other agents with well known anticoagulant inhibitory activity. See, for example, U.S. Patent No. 5,147,638 to Esmon discussed below and the

numerous publications cited therein, which were enclosed with the last response and the Information Disclosure Statement. In response to the statements in the Office Action at page 8 that indicate that the Esmon patent claiming HPC4 supports the uniqueness of HPC4, the Examiner is correct. However, the Examiner has not addressed the disclosure and scope of the claims in the '638 patent nor any of the numerous publications submitted by applicant in support of the breadth of the claims. Mere assertions are not sufficient to rebut objective evidence submitted by an applicant in response to a rejection under §112.

Although the Examiner seems to be concerned regarding the possibility of pathologic thrombosis whenever a systemic thrombogenic drug is utilized, no evidence has been provided that one would expect such a condition to occur. Applicant is an M.D. who is actively treating patients, as well as a researcher, as is Dr. Fass. The consideration of pathologic thrombosis in the application relates to abnormalities associated with congenital deficiencies in protein C, not from the transient inhibition of protein C, as described at page 14, last paragraph. The Examiner's attention is again directed to page 15, wherein lines 29-33 state that titration of the dosage is possible so that inactivation of a specific fraction of the circulating protein C pool is achieved. Dosage titration is well known in the art. Page 16, lines 12-16, describes how normal protein C activity can be reestablished by administering extrinsic "pre"-activated protein C. One skilled in the art could apply one of these procedures for use in conjunction with use of any of the claimed agents if so desired.

Animal antibodies are useful for treatment of humans

The Examiner's argument regarding the use of animal antibodies, based on the opinion of a single author, **who has not been authenticated as an expert**, is contrary to what those skilled in the art believe. Not only are a number of animal antibodies in clinical use as well as clinical trials, no **objective evidence** has been submitted by the Examiner to support the proposition that a single use, as will generally be useful in the claimed method, would elicit any kind of problem. See also Dr. Fass' Declaration.

The Examiner has not responded to applicant's comments and enclosures with the last response (U.S. Patent No. 5,202,253 to Esmon, et al., disclosing at col. 2, lines 62-66 (HPC4 binds to the activation region of human, pig, baboon, and canine protein C; Genetic Engineering News, October 1, 1994; the University Hospital Consortium, UHC Biotechnology Monitor, January 1994, reporting that many antibodies are being developed for use in clinical treatments, including the Centoxin antibody of Centocor; the brochure on "ONCOSCINT CR/OV", "DIGIBIND" Digoxin Immune FAB (ovine), NeoRX product brochure, and articles by Petersen, et al., Amer. J. Surg. 165, 137-143 (January 1993), Markowitz, et al., Clin. Nuclear Med. 18(8), 685-700 (1993).

The application is enabling to one skilled in the art

Dr. Fass is clearly "one skilled in the art". His Declaration, which was uncoached and uncompensated, unequivocally states that he could practice the claimed method and composition based on the application. The examples demonstrate actual reduction to

practice. The Examiner has provided no basis for rebutting the applicant's statements in the application as to the methods of use.

With regard to the order of administration, the Examiner should understand that one of the problems with microvascular bleeding is that there is ongoing generation of activated protein C; it is not just all activated in a matter of seconds and then no more is generated. This is in fact one of the major reasons it is difficult to stop. Accordingly, there is no reason the claims should be limited to administration before bleeding has begun - which is also rather impractical since one rarely presents for treatment **prior** to injury!

With regard to the ongoing availability of the HPC4 antibody the Examiner's attention is drawn to the enclosed copy of In re Argoudelis 434 F.2d. 1390 (C.C.P.A. 1970), where the Court states at page 1394:

> (1) There is always the possibility that sometime after the issuance of a patent, the disclosure which was initially enabling may become 'unenabling' and (2) whether a given disclosure which identifies a material to be employed in the practice of the claimed invention is 'enabling' within the meaning of 35 U.S.C. 112, . . . the court concluded that the possiblity that at a future date one skilled in the art might no longer be enabled to practice the invention was too speculative to justify a holding that the disclosure was insufficient under § 112. (In re Metcalfe, 410 F.2d 1378, 56 CCPA 1191 (1969)) . . . Applying the same considerations in the present case, we note that (1) a public depository was used; . . . (3) the depository is under a contractual obligation to place the culture in the permanent collection , to supply samples to person legally entitled . . . We conclude that the possibility that the disclosure may someday become non-enabling is even more speculative than in Metcalfe, and hence does not render the disclosure insufficient under § 112.

Indefiniteness

Claims 14-16 defines a composition having two components. If the rejection is based on non-enablement, it should be clearly stated. This rejection has been addressed above. Dr. Fass, one of ordinary skill in the art, has declared under oath that he would be able to practice the claimed method and composition as described in the application. The claim is intended to encompass two components whether in a single container or in two containers. This is not indefinite. There is a rule of common sense in reading claims - the standard is whether they are indefinite to one of ordinary skill in the art - not whether they can be twisted and misinterpreted to cover any conceivable embodiment that might not work. Applicant has met this burden.

The same arguments apply to the term "prevent anticoagulation". One of ordinary skill in the art would know that protein C is a naturally occurring anticoagulant; the claim requires administration of an inhibitor of protein C, therefore it would be clear to one of ordinary skill in the art of coagulation what the phrase "prevent anticoagulation" means.

Claim 19 has been amended to correct the dependency.

Rejections under 35 U.S.C. §103

Claims 1-3, 7, 11-13, and 20-21 were rejected under 35 U.S.C. § 103 as obvious over U.S. Patent No. 5,202,253 to Esmon et al. Claim 4 was rejected under §103 as obvious over Esmon et al., in combination with U.S. Patent No. 5,130,244 to Nishimaki, et al. Claims 5, 6, 8, 9, 14-16, and 19 were rejected under §103 as obvious over Esmon, et

al, in combination with Nishimaki, et al., and Furie, et al., Cell 53, 505-518 (1988). These rejections are respectfully traversed.

Esmon, et al.

Esmon, et al. discloses and claims an antibody immunoreactive with protein C. There is no disclosure of using the antibody to inhibit microvascular bleeding. Instead, the disclosure clearly indicates that the antibody is useful for **normalization** of bleeding and clotting.

The Examiner's attention is again drawn to the second Esmon patent, of which applicant is a co-inventor, and numerous publications which have been submitted and apparently not considered. These indicate that the antibody is not only useful for normalization of bleeding, but that clotting can be initiated in solid tumors **but no where else in the body**. As discussed by Dr. Comp during the telephone interview, there was no clotting in the animals to whom HPC-4 was administered **except in the tumors**. There were no strokes, heart attacks or kidney damage, which would be indicative of clotting elsewhere in the body. The Examiner has made no attempt to rationalize the apparent inconsistency in these results with what applicant is claiming. Specifically, it would not be obvious from a patent which discloses that HPC-4 is useful for normalization of bleeding and clotting, and inducing clotting in solid tumors but no where else in the body, that it could also be used to stop microvascular bleeding.

U.S. Patent No. 5,130,244 to Nishimaki et al.

Nishimaki, et al., merely discloses a sugar stabilized aqueous thrombin preparation. There is nothing regarding using the topically applied preparation in combination with anything else, much less a systemically administered anti- natural anticoagulant.

Furie, et al.

Furie et al. reviews the coagulation cascade. There is nothing regarding combining a topically applied coagulant preparation in combination with anything else, much less a systemically administered anti- natural anticoagulant. In fact, the authors conclude with the statement regarding the complexity of the clotting system and the interaction of soluble components with cell bound components.

The requirement under §103 is that the prior art must disclose each claimed element as well as provide the motivation to combine as applicant has done, with the expectation of achieving the desired result. There is simply no such motivation in the cited art. In fact, as demonstrated by the Declaration of Dr. Fass, the numerous publications submitted by applicant, and the '638 patent to Esmon, et al., the prior art **teaches away from** applicant's claimed method and composition.

Allowance of claims 1-9, 11-16 and 19-21, as amended, is earnestly solicited.

Respectfully submitted,

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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)

I hereby certify that this Amendment, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Date: February 27, 1996

Patrea L. Pabst

APPENDIX: *Claims as Amended*

1. (three times amended) A method for inhibiting microvascular bleeding at a site in a patient exhibiting microvascular bleeding comprising administering to the patient a compound in a pharmaceutically acceptable carrier in an effective amount to prevent anticoagulation by greater than 90% of activated protein C in human plasma, wherein the compound is an inhibitor of an anticoagulant selected from the group consisting of protein C, antithrombin III, heparin cofactor II, thrombomodulin and tissue factor pathway inhibitor.

2. (amended) The method of claim 1 wherein the anticoagulant is protein C.

3. The method of claim 1 wherein the inhibitor is administered systemically.

4. The method of claim 1 wherein the inhibitor is administered topically.

5. (amended) The method of claim 1 further comprising topically administering at the site of the bleeding a coagulant.

6. The method of claim 5 wherein the coagulant is selected from the group consisting of thrombin and tissue thromboplastin.

7. (amended) The method of claim 2 wherein the inhibitor is an antibody to protein C.

8. (twice amended) The method of claim 7 wherein the inhibitor is administered systemically further comprising the step of topically administering a coagulant at the site of bleeding.

9. The method of claim 8 wherein the topically administered coagulant is selected from the group consisting of thrombin in a dosage of between approximately 1000 and 10,000 units and tissue factor in a dosage of between approximately 0.1 and 10 mg.

11. (amended) The method of claim 1 wherein the inhibitor is administered to a burn patient.

12. (amended) The method of claim 1 wherein the inhibitor is administered to a patient with tissue or skin grafts.

13. (amended) The method of claim 1 wherein the inhibitor is administered to a patient with cerebral contusions.

14. (Three times amended) A composition for inhibition of microvascular bleeding comprising as a first component an inhibitor of a natural anticoagulant selected from the group consisting of protein C, thrombomodulin, antithrombin III, heparin cofactor II and tissue factor pathway inhibitor in a pharmaceutically acceptable carrier for systemic administration to a patient and as a second component a coagulant in a pharmaceutically acceptable carrier for topical administration to a patient.

15. The composition of claim 14 wherein the inhibitor specifically inhibits protein C.

16. The composition of claim 14 wherein the coagulant is selected from the group consisting of thrombin and tissue thromboplastin.

19. (twice amended) The method of claim [18] 4 further comprising the step of topically administering a coagulant at the site of bleeding.

20. The method of claim 3 wherein the inhibitor is a monoclonal antibody immunoreactive with protein C and blocking protein C activation.

21. The method of claim 20 wherein the inhibitor is HPC-4, deposited with the American Type Culture Collection, Rockville, MD and assigned ATCC No. 9892.